

Primary hyperparathyroidism: 7,000 years of progress

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■ ABSTRACT

Because of widespread screening of the serum calcium concentration, most patients with primary hyperparathyroidism now present with very mild disease instead of the severe bone or kidney manifestations seen in the past. The US National Institutes of Health (NIH) in their 2002 guidelines recommend surgery for patients with symptoms and for select patients without symptoms. But many now argue that all patients with primary hyperparathyroidism should be referred for surgery to reduce fracture risk and enhance general health.

S EVEN THOUSAND years ago, in what is now Germany, lived a woman whose skeleton, recently analyzed using modern methods, shows the pathognomic lesions of primary hyperparathyroidism.¹

Although nowadays primary hyperparathyroidism is usually diagnosed before obvious bone and renal manifestations occur, even very mild disease is associated with increased risk of fracture and cardiovascular disease, and most patients can benefit from parathyroidectomy.

This article discusses the physiology, diagnosis, and management of primary hyperparathyroidism.

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■ NOT UNCOMMON IN OLDER WOMEN

Primary hyperparathyroidism is not uncommon in the United States, affecting about 10 to 30 people per 100,000. The prevalence in some other countries is much higher: in Italy and Sweden up to 2% of women over age 55 years may be affected. Women develop it three times more often than men, and because it often develops around the time of menopause, primary hyperparathyroidism should be considered whenever evaluating a woman for osteoporosis.

■ CAUSES 'STONES, BONES, GROANS'

The parathyroid glands synthesize and release parathyroid hormone (PTH) in an amount inversely proportional to the concentration of ionized calcium in the blood.

PTH has several actions in different organs. In the kidney, it decreases tubular reabsorption of phosphorus, leading to increased urinary phosphorus excretion and reduced serum phosphorus. Also in the kidney, it increases the generation of calcitriol, the active form of vitamin D (1,25-dihydroxyvitamin D), which increases calcium and phosphorus absorption in the gastrointestinal tract. In bone, PTH activates bone resorption, releasing calcium and phosphorus into the blood. Bone resorption is also augmented by the actions of calcitriol. Together, these actions result in slightly increased serum concentrations of calcium and phosphorus, although the increase in phosphorus is offset by its enhanced excretion in the kidney.

The clinical syndrome of primary hyperparathyroidism can be easily remembered as "stones, bones, abdominal groans, and psychic

Consider
primary
hyperpara-
thyroidism
when
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overtones.” It includes renal stones, osteoporosis, peptic ulcer disease, pancreatitis, constipation, fatigue, and depression.

Presentation changed with calcium screening

When blood calcium screening became widely available in the early 1970s, the clinical presentation of primary hyperparathyroidism changed from that of severe bone disease or kidney stones to no symptoms in most cases.²⁻⁴

Serum calcium levels are not routinely measured in children and adolescents, so pediatric patients with primary hyperparathyroidism continue to present with severe symptoms.⁵⁻⁹

Adults with severe hypercalcemia (serum calcium concentration > 13.0 mg/dL), bone pain, or weight loss are more likely to have a malignancy than primary hyperparathyroidism. Neoplasia and primary hyperparathyroidism together account for 90% of all cases of hypercalcemia.

RENAL MANIFESTATIONS

About half of patients with primary hyperparathyroidism have elevated urinary calcium excretion (> 250 mg daily calcium excretion in women and > 300 mg daily in men), and about half of these patients develop renal stones. Serum calcium levels should be checked in any patient with a renal stone: about 5% of women with stones have primary hyperparathyroidism. Nephrocalcinosis and renal failure are uncommon in primary hyperparathyroidism, however.

Patients who develop primarily renal disease rather than bone disease have a slightly different profile: they tend to be younger, have lower serum calcium levels, have lower-weight parathyroid glands, and often have more longstanding disease with fewer manifestations other than renal stones.

Which comes first—the adenoma or the hypercalciuria?

Experts debate whether in most cases a parathyroid adenoma causes hypercalciuria and stone formation, or if the hypercalciuria comes first, caused by a renal calcium “leak,”

leading to secondary hyperparathyroidism and the development of a parathyroid adenoma over time. Although past studies showed that parathyroidectomy cures renal stone disease in almost all cases, more recent studies have shown that stones recur within 5 years in as many as 30% of patients.^{10,11}

Frokjaer and Mollerup¹² measured 24-hour urine calcium excretion at baseline and at 1 to 3 years after parathyroidectomy in patients with primary hyperparathyroidism. Before surgery, the amount of calcium excretion was similar in patients who had renal stones and in those didn't have stones, but postoperatively, more patients who originally had renal stones continued to have some degree of hypercalciuria.

I recommend periodically checking 24-hour urine calcium levels after parathyroidectomy in patients with a history of renal stones.

BONE MANIFESTATIONS

The bone manifestations of primary hyperparathyroidism differ from those of postmenopausal osteoporosis: hyperparathyroidism involves loss of cortical bone (the outermost compact bone), and postmenopausal osteoporosis involves loss of cancellous or trabecular bone (the interior part), especially in the spine and hip.¹³

Bone densitometry is an important tool for detecting osteoporosis due to hyperparathyroidism, to predict future fracture risk, to monitor changes in bone mineral density, and to assess response to therapy.¹⁴⁻¹⁶

In patients with mild primary hyperparathyroidism, bone mass measurement by dual-energy x-ray absorptiometry (DXA) may be normal in the spine, which is relatively enriched in cancellous bone. By contrast, bone density in the distal third of the forearm, which contains a greater proportion of cortical bone, may be markedly reduced. The bone density of the hip (eg, femoral neck) will show an intermediate effect, as the hip is composed of both cancellous and cortical bone. Importantly, this pattern differs fundamentally from the changes that occur in postmenopausal osteoporosis due to estrogen deficiency, in which the preferential loss of cancellous bone leads to a greater reduction of

**Monitor
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surgery
in patients
who had
renal stones**

bone density in the vertebral spine than in the hip or forearm.

In the past, radiographs of the hand were taken to aid in the diagnosis, revealing loss of cortical margins with tunneling resorption and cyst formation at sites of intense bone resorption along the phalanges. However, such findings are evident only in patients with severe disease such as long-standing renal hyperparathyroidism (osteodystrophy), so hand radiography should no longer be routinely done.

PTH can destroy bone—or build it

Excess PTH causes bone disease, but PTH and PTH peptide fragments can also be used to treat osteoporosis. This paradox can be explained by the effect of PTH on expression of different genes that influence osteoclast formation and function in opposite ways: PTH has powerful effects on the receptor activator of the nuclear factor kappa B (RANK) ligand, which activates osteoclasts to break down bone, and on osteoprotegerin (OPG), which is a decoy receptor for the RANK ligand and is protective of bone.

Once-daily injections of PTH increase expression of the transcription factor Runx2, which increases the osteoblast number by attenuating osteoblast apoptosis and thereby increasing bone formation. Intermittent PTH also increases OPG expression and decreases RANK ligand. These effects reduce osteoclast activity. On the other hand, continuous infusion of PTH, as in hyperparathyroidism, has the opposite effect: it increases RANK ligand and reduces OPG, resulting in increased activity of osteoclasts, increased bone resorption, and increased serum calcium.¹⁷

■ OTHER MEDICAL COMPLICATIONS

Primary hyperparathyroidism can lead to a constellation of other problems, ie:

- Cardiovascular disorders due to hypertension
- Diabetes mellitus
- Gastrointestinal disorders, because increased calcium leads to increased gastrin secretion, potentiating gastroesophageal reflux disease. Hypercalcemia also increases secretion of digestive enzymes, leading to pancreatitis.

Some, but not all, studies have shown that even mild primary hyperparathyroidism can cause neuropsychiatric symptoms or even more significant consequences, with patients having overall increased mortality and increased cardiovascular risk because of increased arterial stiffness and hyperlipidemia.^{18–24}

■ PTH AND CALCIUM ARE BOTH ELEVATED

To diagnose primary hyperparathyroidism, both an elevated serum calcium (total or ionized) concentration and an elevated PTH level must be present. Other laboratory findings may include:

- Elevated serum 1,25-dihydroxyvitamin D concentration
- Low serum phosphorus concentration
- Increased urinary calcium excretion
- Decreased tubular reabsorption of phosphorus
- Elevated urinary excretion of nephrogenous cyclic adenosine monophosphate (cAMP).

Serum calcium: Total, protein-bound, and ionized

Hypercalcemia is the most important biochemical feature of primary hyperparathyroidism. Routine screening of normal adults reveals hypercalcemia in 0.5% to 1%. For many, however, it is not true hypercalcemia, but an artifact resulting from an abnormal concentration of blood proteins, especially albumin.

Serum calcium exists in three forms. About 46% is bound to proteins, primarily albumin. Another 6% is diffusible and non-ionized and bound to negative ions such as phosphate, citrate, bicarbonate, and lactate. The remaining 47%, which is ionized and diffusible, is the physiologically important form.

These serum calcium concentrations are affected by serum albumin levels and pH.

Serum albumin concentration. When measuring total calcium, it is assumed that circulating protein concentrations are normal. However, a patient with low albumin has a low total calcium level even though the

Hyperparathyroidism reduces cortical bone; postmenopausal osteoporosis reduces trabecular bone



Serum albumin and pH influence the serum calcium concentration

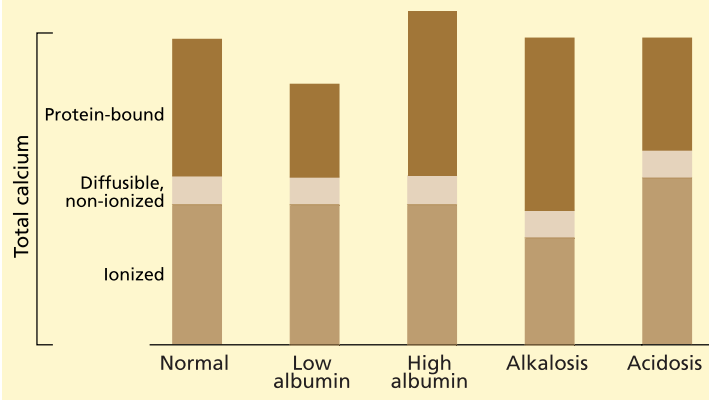


FIGURE 1. Effect of the albumin concentration and pH on total, protein-bound, ionized, and nonionized calcium concentrations. Ionized calcium is the physiologically important fraction.

TABLE 1

Causes of hypercalcemia, by age

From birth to age 20 years

- Familial hypocalciuric hypercalcemia
- Subcutaneous fat necrosis
- Williams syndrome
- Idiopathic hypercalcemia

From older adolescence to age 40 years

- Familial hyperparathyroidism
- Multiple endocrine neoplasia (MEN) type 1

From age 40 years and older

- Parathyroid adenoma
- Neoplasia (cancer of breast, lung, colon, prostate, and kidney, multiple myeloma)

Unusual diagnoses

- Granulomatous disease (sarcoidosis, histoplasmosis)
- Medication-induced (lithium, thiazide diuretics)

amount of ionized calcium is normal. Conversely, a patient with a high concentration of albumin (as commonly occurs during a prolonged blood draw, resulting in local hemoconcentration) or elevated gamma globulin fraction (as in multiple myeloma) has an elevated total serum calcium despite having a normal ionized fraction (FIGURE 1).

To correct for potential errors, 0.8 mg/dL is added or subtracted to the serum calcium concentration for each 1 g/dL of albumin above or below a serum albumin concentration of 4.0 g/dL. For example, suppose a patient has a measured total serum calcium value of 11.0 mg/dL and a serum albumin level of 5.6 g/dL. The calcium seems elevated, but the physiologic effect is equivalent to that of a calcium concentration of 9.7 (11 minus 1.3) mg/dL, which should be used as the “corrected” calcium value.

Serum pH. Alkalosis increases the affinity of albumin for calcium, thereby reducing the proportion of ionized calcium. The low ionized calcium concentration can cause the symptoms of hypocalcemia to occur in patients with normal total serum calcium levels. This often happens in young patients who have developed acute respiratory alkalosis as a result of hyperventilation secondary to anxiety.

The ionized calcium fraction is not routinely measured because it is inconvenient: the blood sample must be processed quickly, as it is for arterial blood gas measurement. Hypercalcemia is usually diagnosed by measuring the total serum calcium concentration, and the ionized component is measured only to confirm hypercalcemia or if the ionized calcium concentration is thought to be elevated despite a normal total concentration.

Hypercalcemia varies in presentation

Hypercalcemia tends to develop from different causes at different ages (TABLE 1).

Clinically, patients with hypercalcemia range from being without symptoms to having life-threatening illness, depending on the degree and duration of hypercalcemia and the blood concentration of ionized calcium.

Measuring PTH

The PTH assay was the breakthrough in diagnosing primary hyperparathyroidism and distinguishing it from tumor-induced hypercalcemia. An elevated serum concentration of PTH with a low serum calcium concentration indicates uremic hyperparathyroidism, and high serum concentrations of both PTH and calcium indicate primary hyperparathyroidism (FIGURE 2).

Free ionized calcium is the physiologically important fraction

Utility of parathyroid hormone measurement

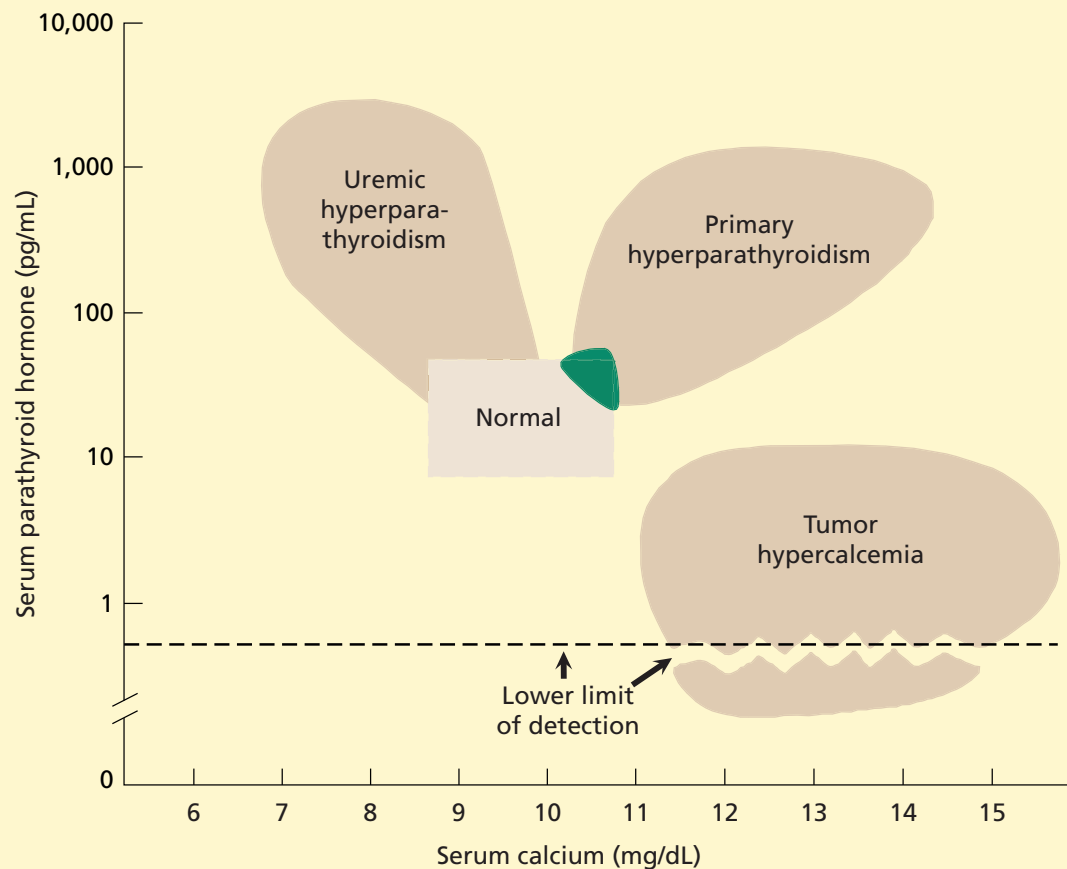


FIGURE 2

Typical two-site PTH immunoassays measure the entire, “intact” PTH hormone, an 84-amino acid chain referred to as PTH (1-84), as well as other circulating fragments with limited or no biological activity. The fragments usually constitute 10% to 30% of the total PTH present, but in renal failure, they may constitute up to 80%. The newest cyclase-activating PTH (CAP) assays measure only the “whole” PTH molecule and may offer increased sensitivity for diagnosing primary hyperparathyroidism.²⁵

Normal circulating levels of intact PTH are typically defined as 10 to 65 pg/mL, but this reference range does not apply to individuals who are younger than 45 years, in whom the normal range is closer to 10 to 45 pg/mL.

PTH levels are now commonly measured in postmenopausal women with osteoporosis,

and this has led to the recognition of a new category of patients: those with elevated PTH levels and normal serum calcium levels. Many of these patients have secondary hyperparathyroidism due to low vitamin D levels, but others have normal vitamin D and normal to high-normal calcium levels and are believed to have incipient primary hyperparathyroidism, which will develop into frank disease in time.

■ SOLITARY ADENOMA IS THE MOST COMMON LESION

Ruda et al,²⁶ in a literature review of more than 20,000 cases of primary hyperparathyroidism, found that 89% of patients had a solitary adenoma and 10% had multiglandular hyperplasia (6% had four-gland disease and 4% had two-gland disease).

Subtract
0.8 mg/dL
from the
total calcium
for each
1 g/dL of
albumin
above 4.0 g/dL



Parathyroid cysts and carcinoma are very unusual, each occurring in fewer than 1% of cases. They typically develop in people in their 30s presenting with severe bone and renal disease. A mass is usually palpable by physical examination.

Pathologists are unable to distinguish histologically between multiple gland hyperplasia and adenoma. In practice, the difference between multiple gland disease and a solitary adenoma is made at surgery by the discovery of more than one enlarged gland, or by inference when hyperparathyroidism is not resolved or recurs after removal of a single parathyroid adenoma.

Familial syndromes

A number of autosomal-dominant syndromes involve multiple-gland parathyroid disease. The two most important to consider, particularly in young people with hypercalcemia and elevated serum PTH concentrations, are familial hypocalciuric hypercalcemia and multiple endocrine neoplasia type 1 (MEN 1).

Familial hypocalciuric hypercalcemia (FHH, also termed benign familial hypercalcemia) affects the parathyroid gland and the kidney. In most patients FHH is due to an activating mutation in the gene encoding the calcium-sensing receptor (CASR). Hypercalcemia is present from birth, but may not be discovered until adulthood.

When diagnosing primary hyperparathyroidism, it is important to identify patients with FHH, because their condition tends not to progress, and therefore they will not need parathyroid surgery. The only potentially dangerous period is during the first few weeks of life, when neonatal severe primary hyperparathyroidism may develop. To identify these patients, one should check the following:

- Urinary calcium excretion, which is very low, typically less than 100 mg per day, with the fractional excretion less than 1%. Patients occasionally have normal or elevated urinary calcium excretion.
- Serum calcium levels in first-degree relatives, because of the autosomal-dominant pattern of inheritance.
- The serum magnesium level, which is higher than in other forms of primary hyperparathyroidism, and the serum PTH level,

which is lower than in typical primary hyperparathyroidism.

MEN 1. More than 95% of patients with MEN 1 have primary hyperparathyroidism with hyperplasia in all four glands, about half have a pituitary tumor, and up to one third have an insulinoma, gastrinoma, or other pancreatic tumor.

The gene responsible for MEN 1 (MENIN) encodes a putative tumor-suppressor protein. Patients with MEN 1 inherit one defective copy of MENIN; subsequent spontaneous loss of the second copy (a “second hit”) leads to development of endocrine tumors. Spontaneous loss of both copies of MENIN can also occur in as many as 35% of sporadic cases of primary hyperparathyroidism, as well as in insulinomas and gastrinomas.²⁷

■ WHICH PATIENTS NEED SURGERY?

Because most patients now present without significant symptoms, a National Institutes of Health (NIH) workshop in 2002 recommended the following as indications for surgical exploration in patients without symptoms²⁸:

- Serum calcium concentration more than 1 mg/dL above normal (> 11.5 mg/dL)
- Bone mineral density more than 2.5 standard deviations below peak bone mass (T score < -2.5) at any site
- Renal stones or urinary calcium more than 400 mg per 24 hours
- Age younger than 50 years
- Patient who cannot be reliably monitored.

Patients without any of these characteristics require only regular monitoring.

The main basis for these recommendations is a 10-year prospective study of more than 121 patients with primary hyperparathyroidism, 101 of whom had no symptoms. Sixty-one patients underwent parathyroidectomy, while 60 underwent monitoring only. Nearly three fourths of the nonsurgical group showed no evidence of progression, including no loss of cortical bone, no worsening of hypercalcemia, and no development of kidney stone disease. The strongest predictor of progression was young age. In addition, patients with a history of nephrolithiasis tended to progress, and patients who were newly

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menopausal had rapid loss of bone mineral density.²⁹

Should guidelines be expanded?

The same study also prospectively compared bone disease using densitometry in patients who had undergone parathyroid surgery vs patients who were monitored only. The monitored patients had little change in bone density after 10 years, but patients who had successful parathyroidectomy had a large increase in bone density in the spine and femoral neck, conferring a significantly reduced risk of fracture.

Vestergaard et al³⁰ compared 674 patients who were operated on for mild or moderate primary hyperparathyroidism with age- and sex-matched controls from a national patient registry. Patients had a rate of fractures 1.8 higher than the controls before the surgery (rate of vertebral fractures, 3.5 times higher; rate of fracture of the ankle and distal part of the lower leg, 2.3 times higher; rate of forearm fractures, 4.0 times higher). Risk decreased to control levels within 1 year after surgery.

Rao et al³¹ randomized 53 patients who had primary hyperparathyroidism without symptoms and did not meet the criteria for surgery for bone density to either undergo parathyroidectomy or be monitored only. Almost all who had surgery had an improved quality of life, a reduction in psychological symptoms, and improved bone density.

This study and others with similar findings^{10,29,32,33} make many question whether the NIH guidelines should be expanded. I argue that they should, especially if the surgeon is experienced and has a greater than 95% success rate. Surgery can be both medically and financially more cost-effective than continuous monitoring over 10 years, especially if new imaging scans are used to locate the adenoma, allowing a minimally invasive unilateral parathyroidectomy rather than a conventional bilateral neck exploration.

■ FINDING ALL THE ADENOMAS

Imaging studies are recommended only if a patient has had a failed parathyroidectomy or is a candidate for a minimally invasive surgical procedure.

Technetium 99m sestamibi imaging, with or without single-photon emission computed tomography (SPECT) enhancement, is the most sensitive test, with from 69% to 91% sensitivity and 98% specificity. The test is only 50% sensitive for multiglandular disease, but this accounts for only about 10% of cases. The scan provides enough information for a single adenoma to be removed under local anesthesia through a minimal incision, and is cost-effective.³⁴ However, it is only marginally useful when a standard four-gland parathyroid exploration will be performed, in which case the best “localization” procedure is the identification by an experienced parathyroid surgeon.

Intraoperative monitoring of PTH. Many surgeons now measure serum PTH concentrations with rapid assays during the operation. If the concentration does not fall by 50% after 5 minutes, a second adenoma is sought.³⁵ Unfortunately, in about one third of cases of double adenomas, although the PTH concentration falls after the first adenoma is removed, hyperparathyroidism recurs within days from the second adenoma. Intraoperative monitoring may be most useful for patients with known multiple adenomas.

■ MEDICAL THERAPY

Medical therapy is used for patients who refuse surgery, who are not candidates for surgery, or who have had unsuccessful parathyroid surgery. Lifestyle recommendations should include the following:

Encourage a normal diet with a normal intake of calcium, but without calcium supplementation. For patients with low levels of 1,25-dihydroxyvitamin D, vitamin D 400 units (as in a multivitamin) per day is reasonable.

Promote exercise. Inactivity increases bone resorption, which may worsen hypercalcemia.

Avoid dehydration, which may worsen hypercalcemia. Powerful diuretics should be avoided.

Medications

Estrogen replacement reduces serum calcium concentration and bone loss. However, because of the risks now known to be associ-

Medical therapy is for those who refuse or cannot have surgery, or if surgery fails



ated with estrogen replacement, it is no longer recommended as a first-line therapy.

Raloxifene reduced serum calcium levels and markers of bone resorption in short-term studies.

Oral bisphosphonates. A series of studies using alendronate 10 mg per day or on alternate days found no significant change in serum or urine calcium concentrations, but found significantly reduced rates of bone resorption (as measured by excretion of urinary *N*-telopeptide) and increased bone density.^{36–38}

Cinacalcet is a calcimimetic, designed to bind to the calcium-sensing receptor on the surface of parathyroid cells, resulting in increased sensitivity of the parathyroid to circulating calcium and reducing PTH secretion.

In a multicenter, double-blind, placebo-controlled study of 78 patients with primary hyperparathyroidism, those treated with cinacalcet 30 to 50 mg per day had reduced serum concentrations of PTH and calcium. Nearly three fourths of patients achieved nor-

mocalcemia within weeks of starting the drug. Effects were maintained over the 52 weeks of the study.³⁹ Other studies have shown a continued response for up to 3 years.

Monitoring

The 2002 NIH guidelines recommend that patients with primary hyperparathyroidism without parathyroid surgery be monitored as follows:

- Serum calcium concentration every 6 months
- Serum creatinine concentration annually
- Bone density of the spine, hip, and forearm annually.

No longer considered necessary are some monitoring studies recommended in older guidelines, eg:

- Abdominal radiography (unless the patient has a history of kidney stone disease)
- 24-hour urinary calcium excretion
- Creatinine clearance.



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